

**We Claim:**

1. A method of delivering a TRPV1 agonist to the epidermis and dermis underlying a 1 cm<sup>2</sup> area of a skin or mucosal surface of a mammal, comprising contacting the area with a composition comprising the TRPV1 agonist and at least one penetration enhancer, wherein 30 minutes after said contacting at least about 3 nmole of the TRPV1 agonist is retained in the epidermis and dermis.

2. The method of claim 1 wherein the TRPV1 agonist wherein 15 minutes after said contacting at least about 3 nmole of the TRPV1 agonist is retained in the epidermis and dermis.

3. The method of claim 2 wherein at least about 32 nmoles is retained.

4. The method of claim 3 wherein at least about 49 nmoles is retained.

5. The method of claim 4 wherein at least about 65 nmoles is retained.

6. The method of claim 5 wherein at least about 16 nmoles is retained.

7. The method of claim 2 wherein the TRPV1 agonist is capsaicin.

8. The method of claim 2 wherein the area contacted is skin.

9. The method of claim 8 wherein the mammal is a human.

10. The method of claim 9 wherein the human suffers from a capsaicin-responsive condition.

11. The method of claim 2 wherein the density of functional nociceptive nerve fibers in the epidermis and dermis is decreased by at least about 20% when measured from 2 to 7 days after said contacting step.

12. The method of claim 2 wherein the composition delivers at least about 3 nmoles of the agonist to skin as measured in a mouse skin absorption assay

13. The method of claim 2 wherein the composition comprises a penetration enhancer selected from the group consisting of ethers, esters, alcohols, fatty acids, fatty acid esters, fatty alcohols, polyols, terpenes, and amines.

14. A method of reducing the density of functional nociceptive nerve fibers in a selected region of a subject, comprising contacting the region with an immediate-release composition that contains a TRPV1 agonist and one or more penetration enhancers, wherein said composition delivers at least about 3 nmoles agonist to skin as measured in a mouse skin absorption assay.

15. A method of reducing the density of functional nociceptive nerve fibers in a selected region of a subject, comprising contacting the region with a composition that contains a TRPV1 agonist and a solvent system comprising one or more penetration enhancers, wherein said composition delivers at least about 3 nmoles agonist to skin as measured in a mouse skin absorption assay, and wherein at least about 5  $\mu$ l composition is delivered to each  $\text{cm}^2$  of the region in about 15 minutes.

16. The method of claim 14 wherein the selected region is on the surface of skin or mucosa.

17. The method of claim 14 wherein said composition delivers at least about 6 nmoles agonist to skin.

18. The method of claim 17 wherein said composition delivers at least about 16 nmoles to skin.

19. The method of claim 18 wherein said composition delivers at least about 32 nmoles to skin.

20. The method of claim 19 wherein said composition delivers at least about 49 nmoles to skin.

21. The method of claim 20 wherein said composition delivers at least about 65 nmoles agonist to skin.

22. The method of claim 21 wherein said composition delivers from about 5 nmoles to about 290 nmoles agonist to skin.

23. The method of claim 14 wherein the depot effect of said contacting is less than about 0.25 as measured in a mouse skin absorption assay.

24. The method of claim 23 wherein the depot effect is less than about 0.1.

25. The method of claim 24 wherein the depot effect is less than about 0.02.

26. The method of claim 25 wherein the depot effect is less than about 0.001.

27. The method of claim 14 wherein the depot effect is in a range of about 0.001 to about 0.25.

28. The method of claim 14 wherein the distribution effect of said contacting is in the range of 0.5 to 2, as measured in a mouse skin absorption assay.

29. The method of claim 14 wherein the composition comprises the TRPV1 agonist and a solvent system, wherein penetration enhancer(s) make up at least 20% (v/v) of the solvent system.

30. The method of claim 29 wherein penetration enhancer(s) make up at least 50% (v/v) of the solvent system.

31. The method of claim 30 wherein penetration enhancer(s) make up at least 90% (v/v) of the solvent system.

32. The method of claim 31 wherein penetration enhancer(s) make up at least 95% (v/v) of the solvent system.

33. The method of claim 14 wherein the solvent system comprises a penetration enhancer selected from the group consisting of ethers, esters, alcohols, fatty acids, fatty acid esters, fatty alcohols, polyols, terpenes, and amines.

34. The method of claim 14 wherein the solvent system comprises a penetration enhancer selected from the group consisting of fatty alcohols and terpenes.

35. The method of claim 14 wherein said solvent system comprises a penetration enhancer selected from the group consisting of l-menthone, dimethyl isosorbide, caprylic alcohol, lauryl alcohol, oleyl alcohol, ethylene glycol, diethylene glycol, triethylene glycol, butylene glycol, valeric acid, pelargonic acid, caproic acid, caprylic acid, lauric acid, oleic acid, isovaleric acid, isopropyl butyrate, isopropyl hexanoate, butyl acetate, methyl acetate, methyl valerate, ethyl oleate, poloxamer, d-piperitone, methylnonenoic acid, methylnonenoic alcohol, and d-pulegone.

36. The method of claim 14 wherein said composition comprises said TRPV1 agonist at a concentration of from 0.05% (w/v) to 60% (w/v).

37. The method of claim 36 wherein the TRPV1 agonist is a vanilloid.
38. The method of claim 37 wherein the TRPV1 agonist is capsaicin.
39. The method of claim 36 wherein said composition comprises said TRPV1 agonist at a concentration of from 1% (w/v) to 20% (w/v).
40. The method of claim 14 wherein the subject is a human.
41. The method of claim 14 wherein said contacting is by topical application or instillation.
42. The method of claim 14 wherein a 15 minute application of the composition to skin of a mammal results in a decrease in the density of functional nociceptive nerve fibers by at least about 50%, wherein the mammal is selected from the group consisting of a mouse or a human.
43. The method of claim 14 wherein the subject is a human.
44. The method of claim 43 wherein the subject suffers from a capsaicin-responsive condition.
45. The method of claim 44 wherein the capsaicin-responsive condition is neuropathic pain, pain produced by mixed nociceptive and neuropathic etiologies, inflammatory hyperalgesia, vulvodynia, interstitial cystitis, overactive bladder, prostatic hyperplasia, rhinitis, rectal hypersensitivity, burning mouth syndrome, oral mucositis, herpes, prostatic hypertrophy, dermatitis, pruritis, itch, tinnitus, psoriasis, warts, skin cancers, headaches, or wrinkles.
46. A method of treating a capsaicin-responsive condition in a subject, comprising non-occlusive or non-adherent administration of a composition that contains a

TRPV1 agonist and at least one penetration enhancer, wherein said composition delivers at least about 3 nmoles agonist to skin as measured in a mouse skin absorption assay.

47. A method of treating a capsaicin-responsive condition in a subject, comprising administration of a composition that contains a TRPV1 agonist and at least two penetration enhancers, wherein said composition delivers at least about 3 nmoles agonist to skin as measured in a mouse skin absorption assay.

48. The method of claim 46 wherein the composition is applied to an area on the surface of skin, mucosa, or endothelium.

49. The method of claim 46 wherein said composition delivers at least about 6 nmoles agonist to skin.

50. The method of claim 49 wherein said composition delivers at least about 16 nmoles to skin.

51. The method of claim 50 wherein said composition delivers at least about 32 nmoles to skin.

52. The method of claim 51 wherein said composition delivers at least about 49 nmoles to skin.

53. The method of claim 52 wherein said composition delivers at least about 65 nmoles agonist to skin.

54. The method of claim 53 wherein said composition delivers from about 5 nmoles to about 290 nmoles agonist to skin.

55. The method of claim 46 wherein the depot effect of said contacting is less than about 0.25 as measured in a mouse skin absorption assay.

56. The method of claim 55 wherein the depot effect is less than about 0.1.
57. The method of claim 56 wherein the depot effect is less than about 0.02.
58. The method of claim 57 wherein the depot effect is less than about 0.001.
59. The method of claim 55 wherein the depot effect is in a range of about 0.001 to about 0.25.
60. The method of claim 46 wherein the distribution effect of said contacting is in the range of 0.5 to 2 as measured in a mouse skin absorption assay.
61. The method of claim 46 wherein the composition comprises the TRPV1 agonist and a solvent system, wherein penetration enhancer(s) make up at least 20% (v/v) of the solvent system.
62. The method of claim 61 wherein penetration enhancer(s) make up at least 50% (v/v) of the solvent system.
63. The method of claim 62 wherein penetration enhancer(s) make up at least 90% (v/v) of the solvent system.
64. The method of claim 63 wherein penetration enhancer(s) make up at least 95% (v/v) of the solvent system.
65. The method of claim 46 wherein the solvent system comprises a penetration enhancer selected from the group consisting of ethers, esters, alcohols, fatty acids, fatty acid esters, fatty alcohols, polyols, terpenes, and amines.

66. The method of claim 65 wherein the solvent system comprises a penetration enhancer selected from the group consisting of fatty alcohols and terpenes.

67. The method of claim 66 wherein said solvent system comprises a penetration enhancer selected from the group consisting of l-menthone, dimethyl isosorbide, caprylic alcohol, lauryl alcohol, oleyl alcohol, ethylene glycol, diethylene glycol, triethylene glycol, butylene glycol, valeric acid, pelargonic acid, caproic acid, caprylic acid, lauric acid, oleic acid, isovaleric acid, isopropyl butyrate, isopropyl hexanoate, butyl acetate, methyl acetate, methyl valerate, ethyl oleate, poloxamer, d-piperitone, methylnonenoic acid, methylnonenoic alcohol, and d-pulegone.

68. The method of claim 46 wherein said composition comprises said TRPV1 agonist at a concentration of from 0.05% (w/v) to 60% (w/v).

69. The method of claim 68 wherein the TRPV1 agonist is a vanilloid.

70. The method of claim 69 wherein the TRPV1 agonist is capsaicin.

71. The method of claim 70 wherein said composition comprises said TRPV1 agonist at a concentration of from 1% (w/v) to 20% (w/v).

72. The method of claim 71 wherein a 15 minute application of the composition to skin of a mammal results in a decrease in the density of functional nociceptive nerve fibers by at least about 20% when measured 2 to 7 days after said contacting step.

73. The method of claim 72 wherein a 15 minute application of the composition to skin of a mammal results in a decrease in the density of functional nociceptive nerve fibers by at least about 50% when measured 7 days after said contacting step.



74. The method of claim 14 wherein the the density of functional nociceptive nerve fibers in the epidermis and dermis underlying said region is decreased by at least about 20% when measured 7 days after said contacting step.

75. The method of claim 46 wherein the composition is administered topically.

76. The method of claim 75 wherein the composition is administered by instillation.

77. The method of claim 46 wherein the composition is administered by injection.

78. The method of claim 46 wherein the composition is administered in the form of a microemulsion.

79. The method of claim 46 wherein the capsaicin-responsive condition is neuropathic pain, pain produced by mixed nociceptive and neuropathic etiologies, inflammatory hyperalgesia, vulvodynia, interstitial cystitis, overactive bladder, prostatic hyperplasia, rhinitis, rectal hypersensitivity, burning mouth syndrome, oral mucositis, herpes, prostatic hypertrophy, dermatitis, pruritis, itch, tinnitus, psoriasis, warts, skin cancers, headaches, or wrinkles.

80. The method of claim 79 wherein the neuropathic pain is associated with diabetic neuropathy, postherpetic neuralgia, HIV/AIDS, traumatic injury, complex regional pain syndrome, trigeminal neuralgia, erythromelalgia and phantom pain.

81. The method claim 80 wherein one or two applications of the composition provide persistent relief.

82. The method claim 81 wherein one application of the composition provides persistent relief.

83. The method of claim 46 wherein the composition is administered to an area on the surface of the skin and subsequent to administration the area is cleaned to remove any residual agonist.

84. The method of claim 83 wherein the area is cleaned using a composition containing at least 60% (w/w/) polyethylene glycol.

85. A pharmaceutical composition comprising a therapeutically effective amount of a TRPV1 agonist and one or more penetration enhancers, and optionally one or more additional therapeutically active agents, wherein said composition delivers at least about 3 nmoles agonist to skin as measured in a mouse skin absorption assay, wherein said pharmaceutical composition is in a form suitable for administration to a subject.

86. A pharmaceutical composition comprising a therapeutically effective amount of a TRPV1 agonist and one or more penetration enhancers, and optionally one or more additional therapeutically active agents, wherein said composition delivers at least about 3 nmoles agonist to skin as measured in a mouse skin absorption assay with the proviso that if the TRPV1 agonist is capsaicin, the concentration of capsaicin is greater than 0.05% and less than 20%.

87. The composition of claim 85 comprising more than one penetration enhancer.

88. The composition of claim 85 that comprises a TRPV1 agonist, and optionally one or more additional therapeutically active agents, in a solvent system comprising one or more penetration enhancers, wherein said one or more penetration enhancers, taken together, constitute at least about 50% (v/v) the solvent system.

89. The composition of claim 88 wherein said one or more penetration enhancers, taken together, constitute at least about 75% (v/v) the solvent system.
90. The composition of claim 89 wherein said one or more penetration enhancers, taken together, constitute at least about 95% (v/v) the solvent system.
91. The composition of claim 85 that, as measured by a mouse skin absorption assay, delivers at least about 3 nmoles agonist to skin.
92. The composition of claim 91 that delivers at least about 3 nmoles agonist to skin with a depot effect of less than 0.25.
93. The composition of claim 85 wherein the TRPV1 agonist is capsaicin.
94. The composition of claim 93 comprising 1% to 15% capsaicin.
95. The composition of claim 85 that comprises a local anesthetic.
96. A method of treating a capsaicin-responsive condition in a subject comprising administering a composition of claim 85.
97. The composition of claim 85 that is contained in a microemulsion.
98. A system for treating a capsaicin-responsive condition, the system comprising the composition of claim 85 and non-occlusive and/or non-adherent applicator device for applying the formulation to skin or a mucosal surface.
99. The system of claim 98 wherein the applicator device is pre-filled with the composition.

100. The system of claim 98 wherein the composition is contained in a container separate from the device.
101. The system of claim 98 further comprising measuring marks on the applicator device for assisting a user in determining the amount of the composition in the applicator device.
102. The system of claim 98 wherein the applicator device is a metered dose aerosol, a stored-energy metered dose pump or a manual metered dose pump.
103. The system of claim 98 wherein the applicator device is a sponge, brush, or swab.
104. A kit comprising the system of claim 98 and a cleaning composition for removal of residual agonist.
105. The kit of claim 104 wherein the cleaning composition comprises at least about 60% polyethylene glycol.
106. A TRPV1 agonist microemulsion comprising a composition of claim 98.
107. A method of treating a patient suffering from a capsaicin-responsive condition that affects a body part, comprising immersing the body part within the microemulsion claim 106.
108. The method of claim 107 wherein the affected area of tissue is immersed within the microemulsion for a predetermined length of time.
109. A method of providing a therapeutic bath comprising adding the TRPV1 agonist microemulsion of claim 106 to a basin.

110. A therapeutic bath apparatus comprising a basin capable of receiving an affected area of tissue therein, wherein the basin has a bottom surface and a wall structure extending upwardly therefrom, and wherein the basin contains a fluid comprising the TRPV1 agonist microemulsion of claim 106.

111. A method of reducing the density of functional nociceptive nerve fibers in a selected region of a subject, comprising contacting the region with the TRPV1 agonist microemulsion of claim 106.

112. The method of claim 111 wherein the selected region is bladder endothelium.

113. A method of treating a capsaicin-responsive condition in a subject comprising administration of a TRPV1 agonist microemulsion of claim 106.

114. The method of claim 21 wherein the capsaicin-responsive condition is overactive bladder and the TRPV1 agonist microemulsion is instilled into the bladder.

115. A method for identifying a composition as useful for therapeutic delivery of a TRPV1 agonist to a subject comprising determining the depot effect for a solution consisting of the composition and the TRPV1 agonist, where a depot effect less than 0.2 indicates the composition is useful for therapeutic delivery of a TRPV1 agonist.

116. The method of claim 115 further comprising determining the amount of agonist delivered to skin epidermis and dermis after a specified time when the composition is applied to the skin surface.

117. A method for ranking two or more compositions according to their utility for therapeutic delivery of a TRPV1 agonist to a subject comprising determining for each composition the depot effect for a solution consisting of the composition and the TRPV1 agonist or a different TRPV1 agonist, comparing the values obtained for each

composition, and ranking them compositions according to the values, where a composition with a lower value is ranked more suitable for therapeutic delivery of the TRPV1 agonist. In one embodiment, there is a further step of determining, for each composition, the amount

118. A pharmaceutical composition comprising capsaicin and methylnonenoyl alcohol or methylnonenoic acid.

119. A method of increasing the amount of a molecule applied to a skin or mucosal surface that enters the underlying epidermal and dermal layers by applying the molecule in a composition comprising methylnonenoyl alcohol or methylnonenoic acid.

120. The method of claim 119 wherein the molecule is a therapeutically active agent.

121. The method of claim 120 wherein the molecule is a TRPV1 agonist.